

UTILITY PATENT APPLICATION TRANSMITTAL

(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
PENN-0701

Total Pages in this Submission

TO THE ASSISTANT COMMISSIONER FOR PATENTS

Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

Methods for Treatment of Cutaneous T-cell Lymphoma

and invented by:

Alain H. Rook

If a **CONTINUATION APPLICATION**, check appropriate box and supply the requisite information:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: _____

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Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 12 pages and including the following:
 - a. ☒ Descriptive Title of the Invention
 - b. ☒ Cross References to Related Applications (if applicable)
 - c. ☐ Statement Regarding Federally-sponsored Research/Development (if applicable)
 - d. ☐ Reference to Microfiche Appendix (if applicable)
 - e. ☒ Background of the Invention
 - f. ☒ Brief Summary of the Invention
 - g. ☐ Brief Description of the Drawings (if drawings filed)
 - h. ☒ Detailed Description
 - i. ☒ Claim(s) as Classified Below
 - j. ☒ Abstract of the Disclosure

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Application Elements (Continued)

3. ☐ Drawing(s) *(when necessary as prescribed by 35 USC 113)*
a. ☐ Formal b. ☐ Informal Number of Sheets _____
4. ☒ Oath or Declaration
a. ☐ Newly executed *(original or copy)* ☒ Unexecuted
b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*
c. ☒ With Power of Attorney ☐ Without Power of Attorney
d. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application,
see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference *(usable if Box 4b is checked)*
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. ☐ Computer Program in Microfiche
7. ☐ Genetic Sequence Submission *(if applicable, all must be included)*
a. ☐ Paper Copy
b. ☐ Computer Readable Copy
c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & documents)*
9. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)*
10. ☐ English Translation Document *(if applicable)*
11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
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14. ☒ Certificate of Mailing
☐ First Class ☒ Express Mail *(Specify Label No.):* **EL429958103US**

UTILITY PATENT APPLICATION TRANSMITTAL (Small Entity)

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Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)
16. ☒ Small Entity Statement(s) - Specify Number of Statements Submitted: 1
17. ☐ Additional Enclosures (please identify below):

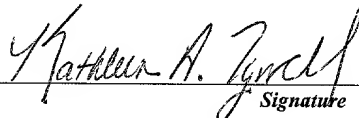
Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	3	- 20 =	0	x \$9.00	\$0.00
Indep. Claims	2	- 3 =	0	x \$39.00	\$0.00
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>					\$0.00
BASIC FEE					\$380.00
OTHER FEE (specify purpose)					\$0.00
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- ☒ A check in the amount of **\$380.00** to cover the filing fee is enclosed.
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- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Dated: **October 15, 1999**


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I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the "BOX Patent Application", Assistant Commissioner for Patents, Washington, D.C. 20231.

- 1) Patent Application Transmittal Letter (2 copies);
- 2) Application consisting of 12 pages of Specification, including one (1) page of Claims, and one (1) page of Abstract;
- 3) Return Post Card;
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Kathleen A. Tyrrell
KATHLEEN A. TYRRELL

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

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Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

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METHODS FOR TREATMENT OF CUTANEOUS T-CELL LYMPHOMA

Introduction

This application claims the benefit of priority from Provisional Application Serial No. 60/104,342, filed October 5 15, 1998.

Background of the Invention

Cutaneous T-cell lymphoma (CTCL) is a lymphoproliferative disorder typically characterized by infiltration of the skin with clonally derived malignant CD4+ T lymphocytes that phenotypically resemble mature T cells (Diamandidou, E. et al. 1996. *Blood* 88:2385-2409). Early presentation of the disease may be confused with eczema, tinea corpus, or psoriasis. Therapeutic efforts are based on the extent of disease, the integrity of the immune system, and the likelihood for progression of disease. Several additional observations which can effect therapeutic decisions include 1) antitumor immune responses mediated by cytotoxic T cells detected in patients with CTCL, 2) biologic response modifiers, which can augment cytotoxic T-cell responses with other specific arms of the antitumor response, such as recombinant interferon- α , are therapeutically active in CTCL, and 3) combinations of potent chemotherapeutic agents do not appear to cure patients with early disease and do not prolong the survival of patients with advanced disease.

For patients with limited or early stage disease, the cell-mediated immune response is usually normal, and the likelihood for serious systemic disease progression is low. Accordingly, these patients can be treated effectively with

a variety of skin-based therapies, including topical mechlorethamine, topical carmustine, and psoralen and ultraviolet A light (PUVA). A significant percentage of patients with such early disease appear to be cured of their
5 disease with these treatments.

Advanced forms of CTCL are not as easily cured, and are often fatal. The patient with advanced forms of CTCL may present with malignancies that progress from plaques to tumors. A more common form of advanced CTCL, Sezary Syndrome
10 (SzS), involves erythroderma occurring throughout the course of disease. In SzS, the malignant cell population, which has an early propensity to localize within the upper dermis, and particularly, within the epidermis (epidermotropism), also becomes nonepidermotropic and is associated with deeper dermal
15 extension and involvement of the peripheral blood. Concurrent with this leukemic, progressive phase of the disease is the onset of progressive immunologic dysfunction. Among the constellation of immune abnormalities that have been noted are increased serum IgE, decreased T cell responses to antigens,
20 impaired cellular cytotoxicity, and peripheral eosinophilia. Associated with these immune abnormalities is a striking deficiency in the ability of peripheral blood mononuclear cells (PBMC) to produce interferon- γ and interleukin-2 in response to activation signals (Rook, A.H. et al. 1993. *Arch.*
25 *Dermatol.* 129:486; Vowels, B.R. et al. 1992. *J. Invest. Dermatol.* 99:90). In contrast to a defect in production of T-helper type 1 (Th1) cytokines, upon stimulation, PBMC from patients with SzS produce increased concentrations of interleukin-4, the levels of which correlate with numbers of
30 circulating malignant T cells (Vowels, B.R. et al. 1992. *J. Invest. Dermatol.* 99:90). The ability to detect T-helper type

2 (Th2) cytokine mRNA (mRNA for interleukin-4 and interleukin-
5) in skin lesions of patients with CTCL, but not in normal
skin (Vowels, B.R. et al. 1994. *J. Invest. Dermatol.* 103:669)
suggests that the malignant Th cells in CTCL may be derived
5 from the Th2 subpopulation of CD4+ cells.

Recent studies have shown that excess interleukin-4
production by PBMCs from SzS patients can be inhibited *in*
vitro either by interferon- γ or by interferon- α (Vowels, B.R.
et al. 1992. *J. Invest. Dermatol.* 99:90). Moreover, SzS
10 patients who develop complete remission associated with the
disappearance of detectable malignant peripheral blood cells
during therapy with biologic response modifiers, including
interferon- α , have restored a normal pattern of cytokine
production by their PBMC in concert with the normalization of
15 many immune parameters (Vowels, B.R. et al. 1993. *J. Invest.*
Dermatol. 100:556). Therefore, strategies directed
simultaneously at affecting the cytokine imbalance and
impeding proliferation of the malignant T cell population may
have a beneficial effect on the outcome of this frequently
20 fatal disorder.

Interleukin-12 (IL-12) is a cytokine that is a powerful
inducer of interferon- γ production and that exerts potent Th1-
inducing effects during the evolution of immunologic responses
against certain microbial antigens (Chan, S.H. et al. 1991.
25 *J. Exp. Med.* 173:869-879; Hsieh, C.S. et al. 1993. *Science*
260:547-549). IL-12 augments Natural Killer (NK) cell
cytotoxicity and cytotoxic T cell proliferation and function
(Hiramatsu, K. et al. 1998. *Cancer Immunol. Immunother.* 46:1-
6; Haku, T. et al. 1997. *Cytokine* 9:846-852; Sahin, U. et al.
30 1996. *Cancer Immunol. Immunother.* 42:9-1), activities that may

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be beneficial in regard to the abnormal Th2 clonal proliferation observed in advanced CTCL, including SzS. Studies have shown that PBMCs isolated from patients with advanced CTCL exhibit marked defects in the production of IL-12 (Rook, A.H. et al. 1997. *Clin. Exp. Immunol.* 107:16-20; Seo, N. et al. 1998. *Clin. Exp. Immunol.* 112:403-409). Further, IL-12 has been shown to have potent antitumor activity in mice with transplantable and primary tumors (Nishimura et al. 1995. *Immunol. Lett.* 48:149-152) and in mice with metastatic residual lymphoma (Verbik et al. 1996. *Clin. Exp. Metastasis* 14:219-229). Brunda and colleagues (1993. *J. Exp. Med.* 178:1223) have demonstrated antitumor activity of IL-12 in mice following both systemic and intralesional administration.

Recent *in vitro* experiments have also shown that the depressed interferon- γ production observed in peripheral blood mononuclear cells isolated from patients with advanced CTCL is normalized by the addition of recombinant IL-12. These *in vitro* studies also showed that the depressed cell-mediated cytotoxicity in CTCL is augmented (Rook, A.H. et al. 1996. *Ann. NY Acad. Sci.* 795:310-318; Rook et al. 1995. *J. Immunol.* 154:1491-1498).

It has now been found that advanced CTCL can be successfully treated in humans by *in vivo* administration of recombinant IL-12.

Summary of the Invention

An object of the present invention is to provide a method for treating advanced cutaneous T cell lymphoma in humans comprising administering to a human an effective amount

of recombinant interleukin-12 so that symptoms of cutaneous T cell lymphoma are reduced.

Another object of the present invention is to provide a combination therapy for treatment of advanced cutaneous T
5 cell lymphoma comprising recombinant interleukin-12 and an adjunct therapeutic agent which stimulates interferon- γ production.

Detailed Description of the Invention

Cytokines are intercellular messenger molecules that
10 evoke biological responses after binding to receptors on responsive cells. A variety of cells of the immune system can secrete cytokines, with the principal producers being the T-helper cells (both type 1, Th1, and type 2, Th2) and macrophages. The binding of cytokines to their receptors on
15 responsive cells leads to numerous physiologic responses including the development of cellular and humoral immunity, induction of the inflammatory response, regulation of hematopoiesis, control of cellular proliferation and differentiation, and induction of wound healing. The
20 complexity of the cytokine pathways and the fact that they exhibit cross-regulation, where the cytokines secreted by one subset of Th cells can block production and activity of cytokines secreted by the other subset, has made it difficult to predict the effect of administration of a single cytokine
25 to a patient.

For example, interferon- γ is secreted by the Th1 subset of Th cells, as well as by NK cells. Increases in the level of interferon- γ results in a depression of activity of Th2 cells. IL-12, which is secreted by macrophages and B-cells,
30 can also inhibit activity of Th2 cells. However, IL-10, which

is secreted by Th2 cells, results in a decrease in activity of Th1 cells, which secrete interferon- γ . This interrelationship of the cytokine pathways makes it difficult to predict the efficacy of *in vivo* administration of a single cytokine in modulating various disease states.

It has now been found, however, that administration of recombinant IL-12 in patients is a safe and effective therapy for advanced CTCL. IL-12 was administered both subcutaneously and intralesionally in a phase I clinical trial of advanced CTCL. A phase I clinical trial is designed to examine both efficacy and safety of a drug.

Patients in the phase I clinical trial were classified as having either extensive plaque (4 patients), SzS (2 patients), or extensive tumors with large cell transformation (2 patients). Patients received either 50, 100, or 300 ng/kg of recombinant IL-12, two times a week for up to 24 weeks. Doses were given both intralesionally and subcutaneously. Subcutaneous dosing resulted in complete responses in 2 of the 4 plaque patients, partial responses in 1 of the 4 plaque patients, and a partial response in 1 of the 2 SzS patients. The overall response rate with subcutaneous dosing (complete and partial responses) was 57%. A minor response was also seen in one of the plaque patients. By "complete response" it is meant complete disappearance of all evidence of disease both clinically and histologically. By "partial response" it is meant that there is at least a 50% decrease (but less than 100%) in size of all measured lesions as compared to their size at the start of therapy. By "minor response" it is meant that there is a 25 to 50% decrease in the size of all measured lesions as compared to their size at the start of therapy.

Following intralesional dosing with recombinant IL-12,

individual plaque, erythema, or tumor regression was seen in most patients (8 out of 9); one patient with SzS dropped out of the trial for personal reasons. Biopsy of regressing lesions revealed a marked decrease in the density of the infiltrate in all cases. Increased numbers of cytotoxic T-cells were observed on immunohistochemical analysis in some biopsies.

Adverse effects associated with recombinant IL-12 treatment, either subcutaneously or intralesionally, were minor and included low grade fever and headache. One patient discontinued IL-12 at week 6 due to depression. These results demonstrated that IL-12 was as safe as well as an effective treatment for advanced CTCL. The results showed that IL-12 may augment antitumor responses. The fact the IL-12 was particularly effective in plaque patients was unexpected and unique.

Accordingly, the present invention provides a useful method for alleviating symptoms and treating CTCL in patients which comprises administering recombinant IL-12 to the patient. The method of the present invention is particularly useful in treating advanced CTCL, which includes patients presenting with plaque, Sezary Syndrome, or tumors with large cell transformation. IL-12 can be administered either systemically (e.g., subcutaneously, intravenously) or intralesionally and can be formulated in any pharmaceutically acceptable carrier which is known to those of skill in the art. For example, an injectable formulation of recombinant IL-12 is made and sold by Genetics Institute (Cambridge, MA). An effective dose of recombinant IL-12 is administered repeatedly, for several weeks, until symptoms of advanced CTCL (such as plaques, tumors or erythroderma) regress or are

reduced. An effective dose is one in which there is at least a partial response in the patient. In some patients a reduction of symptoms of advanced CTCL represents a total absence of those lesions after treatment. Dosage schedules and regimens are routinely designed by those of skill based upon results described above for the phase I trial. In a preferred embodiment, approximately 100 to 300 ng/kg of recombinant IL-12 is administered by subcutaneous or intravenous injection 2 to 3 times per week.

10 The present invention also provides combinational therapies for the treatment of CTCL. It has been found that CTCL may be treated by the combined use of recombinant IL-12 and adjunct therapeutic agents that also induce interferon- γ production. Examples of adjunct therapeutic agents that also induce interferon- γ production include, but are not limited to, retinoids, interleukin-2, interleukin-15, interleukin 18, interferon- α and interferon- γ .

In fact, experiments in peripheral blood monocytes from patients with advanced CTCL indicate that administration of IL-12 in combination with an adjunct therapeutic agent such as interleukin-18 synergistically augment interferon- γ production and cytotoxic lymphocyte activity. In these experiments, PBMC from patients with advanced CTCL and normal healthy volunteers were cultured with medium alone, PHA, interleukin-18 or IL-12 alone, PHA plus interleukin-18 or IL-12, and PHA plus interleukin-18 and IL-12 for 20-48 hours and supernatants were assayed by ELISA for interferon- γ as described by Rook et al. 1995. *J. Immunol.* 154:1491-1498. PBMC were also assayed for NK cell activity using CR51 labeled k562 cells as targets as described by Rook et al. 1995. *J. Immunol.* 154:1491-1498. Interleukin-18 and IL-12 each

significantly increased interferon- γ production by patient and normal PBMC. Interferon- γ production was also synergistically augmented by combining interleukin-18 and IL-12 in culture. Similarly cultures combining interleukin-18 and IL-12 more
5 markedly enhanced NK cell activity in comparison to interleukin-18 and IL-12 alone.

Experiments have also shown that clinically available retinoids, such as acitretin, 13-cis-retinoic acid, and all trans-retinoic acid, in concentrations ranging from 1 to 10
10 ng/ml, induce production of low levels (20 to 100 pg/ml) of interferon- γ in PBMCs from normal volunteers. A number of clinical studies have shown that retinoids have clinical activity in the treatment of CTCL, with response rates ranging from 30% to 60% (Fuss, F.M. and T.M. Kuzel. 1995. *Hematol.*
15 *Oncol. Clin. North Am.* 9:1127-1137). The highest response rates, however, are seen when patients have early stage disease, not advanced CTCL. Retinoids have been suggested as adjunct therapy for treatment of CTCL with interferons or PUVA. In studies in CTCL patients, the all trans-retinoic
20 acid was the most potent retinoid for inducing interferon- γ activity. Addition of anti-IL-12 neutralizing antibodies to the retinoid-cultured cells reduced the interferon- γ -inducing activity of the retinoids (Rook, A.H. et al. 1996. *Ann NY Acad. Sci.* 795:310-318). Thus, at least a portion of the
25 interferon- γ activity of retinoids appears to be mediated through effects on IL-12. Therefore, patients with advanced CTCL can be administered lower doses of recombinant IL-12 in combination with a clinically available retinoid to alleviate or treat CTCL with fewer side effects from administration of
30 IL-12. Dosages of the retinoid to use in the patients can be

selected by one of skill based on clinical use of these drugs for other conditions.

The following nonlimiting examples are provided to further describe the invention.

5 EXAMPLES

Example 1: Administration of rIL-12 to humans

This study was an open-label, nonrandomized, single center, Phase ½ study of recombinant human IL-12 administered by subcutaneous injection in patients with cutaneous T-cell lymphoma (CTCL). Adult male and female patients (age ≥ 18 years) with a histological diagnosis of CTCL for whom there was no standard curative treatment and who met certain inclusion and exclusion criteria were enrolled in the study. Patients were treated on an outpatient basis. However, the initial dose was administered to patients admitted overnight for observation at the Clinical Research Unit. Dose levels of 50 ng/kg, 100 ng/kg and 300 ng/kg were administered two times a week subcutaneously for up to 24 weeks. An initial group of patients was entered at the lower dose (50 ng/kg). Safety at this doses was evaluated for 4 weeks before entering patients at the 100 ng/kg dosing levels. Similarly, an initial group of four patients was entered at the 100 ng/kg dose and safety was evaluated at 4 weeks prior to entering patients at the 300 ng/kg dose range. Total duration of the study was 1 year including 4 months enrollment, maximum 24 weeks of therapy and 2 months follow-up.

1. A method for treatment of advanced cutaneous T cell lymphoma in a human comprising administering to a human an effective amount of recombinant interleukin-12 in a pharmaceutically acceptable carrier.

2. The method of claim 1 further comprising administering an adjunct therapeutic agent which stimulates interferon- γ production.

3. A composition for treatment of advanced cutaneous
T cell lymphoma in a human comprising recombinant interleukin-
12 and an adjunct therapeutic agent which stimulates
interferon- γ production.

[illegible]

Docket No.
PENN-0701

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Methods for Treatment of Cutaneous T-cell Lymphoma

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International Application Number _____ and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	<input type="checkbox"/>
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	<input type="checkbox"/>
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	<input type="checkbox"/>

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

<u>60/104,342</u>	<u>October 15, 1998</u>
(Application Serial No.)	(Filing Date)
<u></u>	<u></u>
(Application Serial No.)	(Filing Date)
<u></u>	<u></u>
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

<u></u>	<u></u>	<u></u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
<u></u>	<u></u>	<u></u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
<u></u>	<u></u>	<u></u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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Second inventor's signature	Date
Residence	
Citizenship	
Post Office Address	